Spinal Cord Diffusion Imaging

Imaging Challenges and Prognostic Value

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Abstract

Short summary of the contents…

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Part I

INTRODUCTION

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Motivation

The spinal cord is a vital part of the human central nervous system (CNS), relaying information to and from the brain and controlling the motor function in the rest of the body. Damage to the spinal cord tissue will compromise signal transmission and can cause severe neurological symptoms, often resulting in a loss of mobility or feeling. Spinal cord injury (SCI) is often caused by trauma, i.e., a mechanical injury of the cord tissue during an accident, fall, etc. However, SCI can also have non-traumatic causes, such as tumours, infectious diseases or degenerative pathologies of the CNS like Multiple Sclerosis (MS).

The introduction of Magnetic Resonance Imaging (MRI) to the clinical practise has vastly improved the diagnosis and treatment monitoring of SCI as it offers a non-invasive way to assess anatomical changes in the spinal cord after injury. While routine MRI scans are aiding the detection of macroscopic changes in the cord, they have a limited prognostic value because of their qualitative nature and because of their lack of specificity in terms of underlying microstructure changes.

The sensitivity of Diffusion Weighted Imaging (DWI) to the diffusion of water molecules in the tissue in vivo has been exploited for more than 20 years to characterise the white matter tissue structure of the brain. Thanks to technological advances such as multi-channel coils for parallel imaging methods and 3T scanners, the past couple of years have made their application of DWI in the spinal cord (SC) more feasible. As a result, diffusion imaging techniques are emerging as useful clinical for methods for visualization and quantification of spinal cord damage. Despite encouraging initial results, much work need still to be done to bring DWI in the cord to clinical practise. Specifically there is the need for in-vivo imaging biomarkers for human SC examinations, which are sensitive to underlying tissue changes and which are capable of quantifying structural and functional pathologies.

1.1 Problem statement

Despite some development work on DWI for SC, the following problems are mainly unresolved

1. Current state-of-the-art DWI analysis methods, such as Diffusion Tensor Imaging (DTI), are unspecific to individual microstructural changes and therefore only have limited value in the evaluation of treatment and recovery in spinal cord pathology. Research on more advanced DWI techniques is usually focussed on the only the brain in mind and is often not directly applicable to the SC in the same manner.

2. DWI acquisition itself is well established in the brain, but much less so in the SC. The SC is a more challenging structure to study because of several problems: the breathing motion, the artefacts arising from the surrounding bones, the pulsation of the cerebro-spinal fluid (CSF) and last but not least its limited size that requires high resolution.

The key motivation of this work is to overcome the challenges above by optimising the whole process from the acquisition design to the analysis methods, based on known SC tissue properties and to develop imaging biomarkers can provide insight in underlying mechanisms of tissue damage and functional recovery.

1.2 Aims

1. Investigate existing DWI methods and identify suitable metrics for SC characterisation

2. Optimise existing acquisition protocols and analysis methods to improve sensitivity to SC pathologies

3. Design new DWI imaging protocols and white matter models and derive new imaging biomarkers specifically for a better quantification of SC microstructure properties

1.3 Summary of contributions

The work presented in this dissertation is divided in three parts, comprising 8 different experiments in total. Each part contributes towards the aims described above as follows:

Part ii shows two studies that use the well established DTI method.

Chapter 2 devises a novel imaging protocol to visualise and quantify the presence of collateral sprouting fibres at different levels of the SC. This experiment contributes towards project aim 1 and 2 as we investigate two different DWI metrics from existing literature and focus on the optimisation of the acquisition protocol.

In Chapter 3 we develop a novel post-processing method that corrects average DTI metrics for partial volume effects. This experiment contributes towards project aim 2, as we aim to improve reliability and reduce inter-subject variability for DTI acquisitions and measurements that are widely used in clinical studies.

Part iii presents two studies which implement the less commonly used q-space imaging (QSI) method in the cord. The aim is to test whether is is possible to distinguish different parts of the healthy human cord by their QSI parameters. The two experiments contributes towards project aim 1 as they test the use of QSI metrics for the investigation of SC microstructure. The experiments also contribute to project aim 3 as they look for the first time into QSI parallel to the major fibre direction as an additional imaging marker.

Chapter 4 presents data that was analysed retroactively on already acquired QSI-data. This dataset data revealed interesting results, but was put in question by technical limitations of the acquisition and analysis method.

Chapter 5 presents our effort to reproduce the results of Chapter 4 on our newly installed 3T scanner, which allowed us more control over the scan parameters than before.

Part iv shows our work towards project aim 3 by developing DWI protocols that allow direct estimation of axon diameter and density of SC white matter tissue. Our $\mathcal{SF}$ method is an extension of the "ActiveImaging" framework by Alexander et al. (2010), which we modify to be able to exploit the characteristic a-priori know single major fibre orientation in structures like the SC. To aid the initial development we use in some experiments the corpus callosum as a model system of highly coherent white matter structures, similar to the SC organisation.

Chapter 6 presents a first implementation of the $\mathcal{SF}$ method. We use synthetic dataset from computer simulations to evaluate our method and compare with Alexander's original method and

further show results of a first real-world implementation of our method applied to ex-vivo monkey spinal cord.

Chapter 7 introduces several improvements to our first $\mathcal{SF}$ implementation and presents a first implementation of the $\mathcal{SF}$ method in-vivo on a standard clinical scanner on two healthy volunteers.

Chapter 8 brings together our efforts in improving image quality and DWI acquisition protocols. We here devise a novel imaging and analysis pipeline for $\mathcal{SF}$-ActiveImaging and assess its scan/rescan reproducibility in the human corpus-callosum. Furthermore, we also present a first application of $\mathcal{SF}$ to the healthy in-vivo human cord in one subject.

Part II

DTI STUDIES

2

Position dependency of radial diffusivity in the cervical spinal cord

3

Fuzzy partial volume correction of average DTI metrics in the spinal cord

Part III

Q-SPACE IMAGING STUDIES

4

QSI in the in-vivo human spinal (I)

5

QSI in the in-vivo human spinal (II)

Part IV

ACTIVE IMAGING STUDIES

6

SF-Active Imaging - An extension of ActiveImaging for single fibre structures

7

In-vivo application of $\mathcal{SF}$-ActiveImaging in human corpus callosum

8

Feasibility and reproducibility of $\mathcal{SF}$-ActiveImaging in human corpus callosum and spinal cord

9

Conclusions

The overarching aim of this dissertation was to develop imaging markers that can be helpful in the clinical assessment of spinal cord pathologies such as traumatic SCI and MS. In several studies we have explored both established methods such as apparent diffusion coefficient (ADC) and DTI as well as more experimental approaches such as QSI and the ActiveImaging framework.

In Chapter2 we have devised a new imaging protocol to visualize and quantify collateral nerves in the cord with DTI. While the size of the study was small, we developed a sound methodical framework for DTI acquisition and processing in the cord, which proved helpful for any analysis of SC data beyond the scope of the study itself. The observations in this study also lead to the development of a novel partial volume correction method for whole cord averages of whole-cord DTI metrics. We showed our PVA correction helps to reduce bias in average whole cord DTI metrics and improves inter-subject variability. The achievable resolution in SC DWI is low and PVA is a common problem to all SC DWI techniques.

In Chapters 4& 5 we turned towards QSI, which offers the theoretically the most complete discription of the diffusion process in any tissue. However, in practise the setup and analysis of in-vivo QSI is very challenging, and only few QSI studies of QSI have been reported in-vivo human SC so far. For the first time we presented here a systematic study of inter- and intra-subject variability of QSI measures over the whole cord area and specific white matter tracts in cervical cord. We demonstrate that variability and reproducibility of QSI metrics is very good, and, as shown in Chapter 5, can be improved even more when combined with modern scanner hardware and a carefully optimised SC imaging set-up. We were unable to reproduce the clear distinction between WM tracts in the cord as seen in ex-vivo high-field MRI experiments by **?**. However QSI metrics in different white matter tracts complemented conventional ADC estimates when distinguishing features of different white matter tracts. While we

were not able to demonstrate a clear advantage of QSI in healthy SC here over conventional analysis, QSI might be more senstitive to WM damage such as Wallerian degeneration, as shown by **?** in a rat axotonomy model. Future work will explore the feasibility QSI to such SC pathologies in-vivo under realistic clincial condition, in a similar fashion to our study of healthy SC we presented here. The protocol presented in Chapter 5 is currently used as part of a longitudinal study of MS patients.

Finally, we presented in Chapters 6&–8 a new imaging method, that is specifically designed to provide direct estimates of axon diameter and density indices in structures with known single fibre orientation such as the SC. We thoroughly evaluated our method, going from using computer simulation via ex-vivo monkey spinal cord samples to application in live humans, first in the corpus callosum and finally the spinal cord. We demonstrate that we our method produces very repeatable maps of axon diameter and axon density indices with very good SNR. However, the key achievement here is that our proposed protocol can be acquired in $\approx$30 minutes, which is crucial for future adoption into clinical studies. Our method extends naturally to different models or imaging sequences. We intend to extend the algorithm the contraint of strictly unidirectional fibre directions to incorporate some degree of dispersion for a more realistic representation of healthy and pathologic white matter. We are also planning to use our protocols to study ex-vivo healthy and MS human cord to better understand the role of our parameter estimates in the presence of tissue alteration. In the long term, our method must be evaluated in the context of a larger clinical study, e.g., of SCI to determine further it's clinical benefit for SC disease diagnosis and management purposes.

A common theme that emerged from all the work we presented here is the importance of a holistic approach in optimising the imaging pipeline to the desired DWI method and vice versa. We have demonstrated the clear benefits of adapting the acquisition protocol to the specific DWI analysis (e.g. in Chapter 2 and Chapter 6). On the other hand we have also shown, e.g. in Chapters 5 and Chapter 8) that a careful optimisation of the imaging parameters themself, such as image quality and positioning are equally important for any successful DWI study. We believe that our contributions meet the initial goal of this thesis to improve existing

acquisition protocols and analysis methods devise new imaging biomarkers for the study of SC with diffusion MRI.

Bibliography

Aboitiz, F., Scheibel, A. B., Fisher, R. S., & Zaidel, E. (1992). Individual differences in brain asymmetries and fiber composition in the human corpus callosum. *Brain Research*, *598*(1-2), 154â 161.

Alexander, D. C., Hubbard, P. L., Hall, M. G., Moore, E. A., Ptito, M., Parker, G. J. M., & Dyrby, T. B. (2010). Orientationally invariant indices of axon diameter and density from diffusion MRI. *NeuroImage*.

Avram, A. V., √ñzarslan, E., Sarlls, J. E., & Basser, P. J. (2012). In vivo detection of microscopic anisotropy using quadruple pulsed-field gradient (qPFG) diffusion MRI on a clinical scanner. *NeuroImage*, (0).
URL http://www.sciencedirect.com/science/article/pii/S1053811912008567

Barazany, D., Basser, P. J., & Assaf, Y. (2009). In vivo measurement of axon diameter distribution in the corpus callosum of rat brain. *Brain*.

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system - a technical review. *NMR in Biomedicine*, *15*(7-8), 435â 455.

Colvin, D. C., Yankeelov, T. E., Does, M. D., Yue, Z., Quarles, C., & Gore, J. C. (2008). New insights into tumor microstructure using temporal diffusion spectroscopy. *Cancer Research*, *68*(14), 5941–5947.
URL http://cancerres.aacrjournals.org/content/68/14/5941.short

Cook, P., Bai, Y., Nedjati-Gilani, S., Seunarine, K., Hall, M. G., Parker, G. J. M., & Alexander, D. C. (2006). Camino: open-source diffusion-MRI reconstruction and processing. In *Proceedings 14th Scientific Meeting, International Society for Magnetic Resonance in Medicine*, (p. 2759).

Does, M. D., Parsons, E. C., & Gore, J. C. (2003). Oscillating gradient measurements of water diffusion in normal and globally ischemic rat brain. *Magnetic Resonance in Medicine*,

49(2), 206,Äì215.
URL http://onlinelibrary.wiley.com/doi/10.1002/mrm.10385/abstract

Drobnjak, I., Siow, B., & Alexander, D. C. (2010). Optimizing gradient waveforms for microstructure sensitivity in diffusion-weighted MR. *Journal of Magnetic Resonance*, *206*(1), 41â 51.

Ferizi, U., Panagiotaki, E., Schneider, T., Wheeler-Kingshott, C., & Alexander, D. C. (2012). White matter models of in vivo diffusion mri human brain data: A statistical ranking. In *16th Conference on Medical Image Understanding and Analysis*.

Huber, P. J. (1996). *Robust Statistical Procedures*. SIAM.

Koch, M. A., & Finsterbusch, J. (2008). Compartment size estimation with double wave vector diffusion-weighted imaging. *Magnetic Resonance in Medicine*.

Komlosh, M., Lizak, M., Horkay, F., Freidlin, R., & Basser, P. (2008). Observation of microscopic diffusion anisotropy in the spinal cord using double-pulsed gradient spin echo MRI. *Magnetic Resonance in Medicine*, *59*(4), 803,Äì809.
URL http://onlinelibrary.wiley.com/doi/10.1002/mrm.21528/abstract

Landis, J. R., & Koch, G. G. (1977). The measurement of observer agreement for categorical data. *Biometrics*, *33*(1), 159.
URL http://www.jstor.org/discover/10.2307/2529310?uid=3738032&uid=2&uid=4&sid=21101301805217

Lätt, J., Nilsson, M., Malmborg, C., Rosquist, H., Wirestam, R., St\aa hlberg, F., Topgaard, D., & Brockstedt, S. (2007). Accuracy of q-space related parameters in MRI: simulations and phantom measurements. *IEEE Transactions on Medical Imaging*, *26*(11), 1437â 1447.

Modat, M., Ridgway, G. R., Taylor, Z. A., Lehmann, M., Barnes, J., Hawkes, D. J., Fox, N. C., & Ourselin, S. (2010). Fast free-form deformation using graphics processing units. *Computer Methods and Programs in Biomedicine*, *98*(3), 278–284.
URL http://www.sciencedirect.com/science/article/pii/S0169260709002533

Ourselin, S., Roche, A., Subsol, G., Pennec, X., & Ayache, N. (2001). Reconstructing a 3D structure from serial histological sections. *Image and Vision Computing*, *19*(1,Äì2), 25–31.

URL http://www.sciencedirect.com/science/article/pii/S0262885600000524

Panagiotaki, E., Schneider, T., Siow, B., Hall, M. G., Lythgoe, M. F., & Alexander, D. C. (2012). Compartment models of the diffusion MR signal in brain white matter: A taxonomy and comparison. *NeuroImage*, *59*(3), 2241â 2254.
URL http://www.sciencedirect.com/science/article/pii/S1053811911011566

Pell, G. S., Briellmann, R. S., Waites, A. B., Abbott, D. F., Lewis, D. P., & Jackson, G. D. (2006). Optimized clinical t2 relaxometry with a standard CPMG sequence. *Journal of Magnetic Resonance Imaging*, *23*(2), 248,Äì252.
URL http://onlinelibrary.wiley.com/doi/10.1002/jmri.20490/abstract

R Core Team (2012). *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0.
URL http://www.R-project.org/

Shrout, P. E., & Fleiss, J. L. (1979). Intraclass correlations: Uses in assessing rater reliability. *Psychological Bulletin*, *86*(2), 420–428.

Siow, B., Ianus, A., Drobnjak, I., Lythgoe, M. F., & Alexander, D. C. (2012). Optimised oscillating gradient diffusion mri for the estimation of axon radius in an ex vivo rat brain. In *Proceedings 20th Scientific Meeting, International Society for Magnetic Resonance in Medicine*.

Tristán-Vega, A., Garcia-Pérez, V., Aja-Fernández, S., & Westin, C.-F. (2012). Efficient and robust nonlocal means denoising of MR data based on salient features matching. *Computer Methods and Programs in Biomedicine*, *105*(2), 131–144.
URL http://www.sciencedirect.com/science/article/pii/S0169260711002021

Wang, J., Zamar, R., Marazzi, A., Yohai, V., Salibian-Barrera, M., Maronna, R., Zivot, E., Rocke, D., Martin, D., Maechler, M., & Konis., K. (2012). *robust: Insightful Robust Library*. R package version 0.3-19.
URL http://CRAN.R-project.org/package=robust

Wilm, B., Svensson, J., Henning, A., Pruessmann, K., Boesiger, P., & Kollias, S. (2007). Reduced field-of-view MRI using

outer volume suppression for spinal cord diffusion imaging. *Magnetic Resonance in Medicine*, *57*(3), 625â 630.
URL http://onlinelibrary.wiley.com/doi/10.1002/mrm.21167/abstract

Wolak, M. E., Fairbairn, D. J., & Paulsen, Y. R. (2011). Guidelines for estimating repeatability. *Methods in Ecology and Evolution*.

Yeh, C.-H., Tournier, J.-D., Cho, K.-H., Lin, C.-P., Calamante, F., & Connelly, A. (2010). The effect of finite diffusion gradient pulse duration on fibre orientation estimation in diffusion MRI. *NeuroImage*, *51*(2), 743–751.
URL http://www.sciencedirect.com/science/article/pii/S1053811910002090

Zhang, H., Hubbard, P. L., Parker, G. J., & Alexander, D. C. (2011). Axon diameter mapping in the presence of orientation dispersion with diffusion MRI. *NeuroImage*, *56*(3), 1301â 1315.
URL http://www.sciencedirect.com/science/article/pii/S1053811911001376